

Case-Control Study of Colon and Rectal Cancers and Chlorination By-Products in Treated Water¹

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Abstract

This population-based case-control study was conducted in southern Ontario, Canada from 1992 to 1994 to assess the relationship between chlorination by-products in public water supplies and cancers of the colon and rectum. Interviews providing residence and water source histories were completed by 76% of eligible cancer cases and 72% of eligible controls. Supplemental data from municipal water supplies were used to estimate individual exposure to water source, chlorination status, and by-product levels as represented by trihalomethanes (THMs) during the 40-year period before the interview. The analyses included 767 colon cases, 661 rectal cases, and 1545 controls with exposure information for at least 30 of these years (75% of subjects with completed interviews). Among males, colon cancer risk was associated with cumulative exposure to THMs, duration of exposure to chlorinated surface water, and duration of exposure to a THM level ≥ 50 $\mu\text{g}/\text{liter}$ and 75 $\mu\text{g}/\text{liter}$. Males exposed to chlorinated surface water for 35–40 years had an increased risk of colon cancer compared with those exposed for <10 years (odds ratio, 1.53; 95% confidence interval, 1.13–2.09). Males exposed to an estimated THM level of 75 $\mu\text{g}/\text{liter}$ for ≥ 35 years had double the risk of those exposed for <10 years (odds ratio, 2.10; 95% confidence interval, 1.21–3.66). In contrast, these relationships were not observed among females. No relationship was observed between rectal cancer risk and any of the measures of exposure to chlorination by-products. The results of this study should be interpreted with caution because they are only partially congruent with the limited amount of literature addressing this issue.

Received 10/18/99; revised 5/17/00; accepted 5/19/00.

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¹ Supported by the Cancer Bureau of the Laboratory Center for Disease Control, Health Canada and also by the National Health Research and Development Program through a fellowship (to W. D. K.).

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Introduction

Chlorine is the most commonly used chemical for the disinfection of Canadian water supplies. During the chlorination process, chlorine reacts with organic material in the water to produce a complex mixture of halogenated and nonhalogenated by-products, the concentration and distribution of which vary with characteristics of the raw water and the treatment process (1). A large number of halogenated chemical species have been identified, including THMs,³ halogenated acetonitriles, halogenated acids, haloketones, and haloaldehydes (2). THMs are the most frequently occurring by-products (3, 4) and are routinely measured in public water supplies, making them a useful marker of the level of chlorination by-products in treated water.

The association between water chlorination and bladder cancer has been the focus of several individual-based epidemiological studies. There have been fewer investigations of cancers of the colon and rectum, and results from studies have been inconsistent (5). Differences in study methods and the specific array of by-products present in different geographic areas may contribute to inconsistencies in results. Because information is generally lacking on historical levels of chlorination by-products, most studies have been based on characteristics of water source, such as chlorinated surface water that correlate, albeit imprecisely, with the level of chlorination by-products. This study used estimated THM levels in public water supplies to examine the relationship between risk of cancers of the colon and rectum and exposure to chlorination by-products.

Materials and Methods

A population-based case-control study of cancers of the bladder, colon, and rectum was conducted. The study methods have been described previously for bladder cancer (6) and will only be summarized here.

Subjects. Cases were 30–74-year-old residents of southern Ontario, Canada, with a primary cancer of the colon or rectum (International Classification of Diseases 9 site codes 153 and 154; Ref. 7). Pathology reports routinely submitted to the Ontario Cancer Registry identified 1722 colon and 1530 rectal cancer cases diagnosed between September 1, 1992, and May 1, 1994 who were eligible for the study. Of these, consent was obtained from the physician to contact 2507 patients; the physician could not be identified for 35 patients, 404 patients were recently deceased or too ill to be contacted, and physicians would not give consent for 306 patients.

To identify control subjects, households randomly selected from a database of residential telephone listings were contacted and a census of residents was taken. Where eligible residents were identified, one was selected to participate based on fre-

³ The abbreviations used are: THM, trihalomethane; CI, confidence interval; OR, odds ratio.

quency matching to the age-gender distribution of the combined case series (bladder, colon, and rectal cancer cases). Of 10,219 households contacted, 91% provided a census identifying 2768 eligible subjects. Over 90% ($n = 2494$) agreed to have a questionnaire mailed to them.

Exposure Assessment. A questionnaire was mailed to the participants, and responses were recorded by a subsequent telephone interview. Participants were queried regarding demographics (*e.g.*, sex, date of birth, and education), other potential risk factors (*e.g.*, medical history and usual diet before diagnosis), and information pertaining to the primary exposures of interest (*e.g.*, residence, water source history, and usual water consumption). Volume of tap water consumed was calculated from the reported daily consumption of water and of beverages or foods made with water, 2 years before the interview.

A database was created that characterized each water supply in the study area according to source (surface/ground), chlorination status (chlorinated/nonchlorinated), and level of THMs by geographic area and time. This was based on a survey of treatment plants that collected information on water source and characteristics, and treatment practices for the years of operation between 1950 and 1990. Water plant information was obtained for an average day in August in 5-year intervals, and that observation was used to represent water characteristics for the years surrounding that date. A model, based on data from the Ontario Drinking Water Surveillance Program for the years 1986–1992, was developed to predict the THM level in treated water based on water and treatment characteristics recorded in the database and available from the water plant survey. Application of this model using reported source and treatment characteristics provided by the survey resulted in an estimate of THM level for each plant by time period. Water from private wells was assigned a THM concentration of zero because it is not chlorinated.

Individual exposures were assigned by linking subject residence and water source information to the relevant treatment plant data by time and geographic area. Exposures occurring over the 40-year-period preceding 2 years before the subject's interview were considered, and only subjects with ≥ 30 years of known water history were included. Duration of exposure to chlorinated surface water and to water with an estimated summer THM level ≥ 50 and $75 \mu\text{g/liter}$ were calculated by summing the number of years in each exposure category. In addition, THM-years, the sum of the products of continuous estimates of the summer THM level and years at that level, was calculated as an estimate of cumulative exposure.

Statistical Analyses. ORs were used as estimates of the relative risk. For the exposures of primary interest, unconditional logistic regression was used to obtain ORs and 95% CIs adjusted for potential confounders (8). Tests for trend were based on a likelihood-ratio test conducted by assigning an ordinal value to each level of a categorical variable and treating the variable as continuous in a logistic regression model. A likelihood-ratio test was performed to evaluate the interaction between cumulative THM exposure and volume of water consumed.

Age, sex, and dietary intake of energy (total kilocalories) were included in all analyses. Additional potential confounders were identified by using backward stepwise regression to build a parsimonious model predicting risk for each cancer site. The risk factors that were considered for inclusion on the basis of the cancer literature were: body mass index, education, consumption of alcoholic beverages (beer, wine, spirits), coffee consumption, previous medical conditions (history of Crohn's

Table 1 Selected characteristics of subjects who had complete covariate information and water source information for at least 30 of the 40 years before the interview, by case group^a

Variable	Controls ($n = 1524$)	Colon cancer cases ($n = 752$)	Rectal cancer cases ($n = 647$)
Continuous [mean (SD)]			
Age (yr)	61.0 (9.9)	64.1 (8.4)	63.2 (8.9)
Energy (1000 kcal/wk)	10.1 (3.3)	10.6 (3.6)	10.6 (3.5)
Cholesterol (100 mg/wk)	12.8 (5.4)	13.6 (5.7)	13.7 (5.6)
Calcium (500 mg/wk)	11.8 (6.5)	11.8 (6.6)	11.8 (6.1)
Categorical (%)			
Male	62.9	56.0	60.7
Education			
Less than complete high school	38.9	52.9	55.5
Complete high school	21.5	19.4	18.1
Greater than complete high school	39.6	27.7	26.4
Previous medical conditions	1.4	1.7	3.4
Body mass index (kg/m^2)			
Low (<24)	25.1	21.9	22.4
Medium (24–29)	50.4	46.4	46.7
High (>29)	24.5	31.7	30.9
Coffee (cups/wk)			
0	20.1	23.4	20.3
1–21	52.6	56.3	58.4
≥ 22	27.4	20.4	21.3
Alcohol (drinks/wk)			
0	69.2	65.8	72.0
1–7	25.7	28.1	22.6
≥ 8	5.2	6.1	5.4

^a Subject characteristics shown are those that enter the parsimonious model for either colon or rectal cancer.

disease or colitis), and dietary intake of protein, fat, fiber, cholesterol, calcium, and vitamin A. Exclusion of factors from the model was based on a score-test $P > 0.10$, a conservative criterion that ensured that all factors that might confound the relationship of interest were included in the model.

Results

Response Rates. Questionnaires were mailed to 1338 colon and 1169 rectal cancer cases and to 2494 control subjects. Illness, death, or communication barriers prevented 193 colon cases, 133 rectal cases, and 62 controls from participating. Of those remaining, questionnaires were completed by 991 colon cancer cases (87%), 875 rectal cancer cases (84%), and 2118 controls (87%). The overall response rate was 77% and 75% for colon and rectal cases, respectively, calculated as the product of physician consent and case participation. In controls, the overall response rate was 72%, the product of the response to initial contact (*i.e.*, agreed to give a household census, and where an eligible subject was present, agreed to receive a questionnaire) and the response to the telephone interview. The analyses included 767 colon cases, 661 rectal cases, and 1545 controls for whom water information was available for at least 30 of the 40 years before the interview.

Covariates. Controls were more often male (63%) compared with colon cases (56%) and rectal cases (61%). This difference can be attributed to our attempt to frequency match controls to a case series that also included bladder cancer cases, 76% of whom were male. The average age of each case group was slightly older than controls because of the difficulty in identifying older control subjects (Table 1).

Potential confounders included in the parsimonious model

Table 2 ORs and 95% CIs for risk of cancers of the colon and rectum according to exposure to water factors, by sex

Water factor ^a level	Males			Females			P ^c
	Cases	Controls	OR ^b (CI)	Cases	Controls	OR ^b (CI)	
Colon cancer							
Chlorinated (yr)							
0-9	101	270	1.00	109	135	1.00	0.003
10-19	41	84	1.70 (1.07-2.68)	25	67	0.55 (0.32-0.94)	
20-34	107	270	1.33 (0.96-1.86)	84	158	0.85 (0.58-1.24)	
≥35	172	335	1.53 (1.13-2.09)	113	205	0.74 (0.52-1.05)	
THM ≥50 μg/liter (yr)							
0-9	166	411	1.00	161	230	1.00	0.030
10-19	138	318	1.13 (0.86-1.50)	96	193	0.77 (0.55-1.07)	
20-34	85	180	1.31 (0.94-1.81)	53	115	0.63 (0.42-0.93)	
≥35	32	50	1.68 (1.02-2.76)	21	27	1.02 (0.55-1.90)	
THM ≥75 μg/liter (yr)							
0-9	223	545	1.00	193	319	1.00	0.323
10-19	128	298	1.12 (0.85-1.46)	95	182	0.91 (0.66-1.25)	
20-34	44	82	1.49 (0.99-2.26)	27	44	0.92 (0.54-1.56)	
≥35	26	34	2.10 (1.21-3.66)	16	20	1.20 (0.60-2.42)	
THM-years (quartiles) (μg/liter-yr)							
1 (0-583)	99	257	1.00	104	122	1.00	0.002
2 (584-1505)	96	225	1.30 (0.92-1.84)	75	155	0.69 (0.47-1.03)	
3 (1506-1956)	94	240	1.11 (0.78-1.57)	75	144	0.73 (0.49-1.08)	
4 (1957-6425)	132	237	1.74 (1.25-2.43)	77	144	0.65 (0.44-0.97)	
THM-years (continuous) 1000 μg/liter-yr	1.62 ^d	1.47 ^d	1.17 (1.06-1.29)	1.39 ^d	1.51 ^d	0.91 (0.81-1.03)	0.002
Rectal cancer							
Chlorinated (yr)							
0-9	127	270	1.00	70	135	1.00	0.578
10-19	33	84	1.10 (0.69-1.76)	22	67	0.71 (0.40-1.27)	
20-34	102	270	0.98 (0.71-1.36)	60	158	0.89 (0.58-1.37)	
≥35	131	335	0.97 (0.72-1.32)	102	205	1.04 (0.71-1.53)	
THM ≥50 μg/liter (yr)							
0-9	181	411	1.00	122	230	1.00	0.546
10-19	118	318	0.94 (0.71-1.25)	76	193	0.78 (0.55-1.11)	
20-34	77	180	1.07 (0.77-1.49)	45	115	0.73 (0.48-1.11)	
≥35	17	50	0.82 (0.45-1.48)	11	27	0.71 (0.33-1.50)	
THM ≥75 μg/liter (yr)							
0-9	238	545	1.00	147	319	1.00	0.777
10-19	106	298	0.89 (0.67-1.18)	80	182	1.00 (0.71-1.40)	
20-34	36	82	1.08 (0.70-1.68)	18	44	0.81 (0.44-1.47)	
≥35	13	34	0.96 (0.49-1.89)	9	20	0.89 (0.39-2.02)	
THM-years (quartiles) (μg/liter-yr)							
1 (0-583)	118	257	1.00	72	122	1.00	0.186
2 (584-1505)	99	225	1.20 (0.86-1.67)	60	155	0.78 (0.51-1.19)	
3 (1506-1956)	83	240	0.90 (0.63-1.27)	68	144	0.93 (0.61-1.42)	
4 (1957-6425)	93	237	1.03 (0.73-1.44)	54	144	0.69 (0.44-1.06)	
THM-years (continuous) 1000 μg/liter-yr	1.37 ^d	1.47 ^d	0.98 (0.88-1.08)	1.42 ^d	1.51 ^d	0.94 (0.82-1.08)	0.648

^a Calculated over the 40 years before the interview for subjects with ≥30 years of known exposure information.

^b OR (95% CI) for colon cancer adjusted for age; sex; education; body mass index; and intake of energy, cholesterol, calcium, alcohol, and coffee. OR (95% CI) for rectal cancer adjusted for age; sex; education; body mass index; previous medical conditions; and intake of energy, cholesterol, calcium, and coffee.

^c P for interaction with sex.

^d Mean values.

predicting colon cancer risk were education, body mass index, and dietary intake of energy, cholesterol, calcium, coffee, and alcoholic drinks. Compared with control subjects, cases with colon cancer, on average, were less educated, had a higher body mass index, and had a higher intake of energy, cholesterol, and alcohol, but lower intake of coffee.

A similar subset of factors was included in the parsimonious model predicting rectal cancer risk, but consumption of alcoholic drinks was not included and previous medical conditions were included. Cases with rectal cancer, on average, were less educated, were more likely to have a history of Crohn's disease or colitis, had a higher body mass index, and had a higher intake of energy and cholesterol, but lower intake of coffee than controls.

Water Source. Risk estimates for colon cancer according to exposure to various water factors differed between the sexes (Table 2). Increasing exposure to each water factor was associated with increasing risks of colon cancer only among males. Among males, each risk factor displayed a trend of increasing colon cancer risk across categories of increasing exposure, which reached at least a 53% elevation in risk for the highest exposure categories. Long-term (≥35 years) exposure to a THM level of ≥75 μg/liter was associated with a doubled colon cancer risk among males (OR, 2.10; 95% CI, 1.21-3.66). The highest quartile of cumulative THM-years exposure was associated with an OR of 1.74 (95% CI, 1.25-2.43). The continuous representation of cumulative THM exposure was associated with a 17% increase in risk for each 1000 μg/liter-years (95%

Table 3 ORs and 95% CIs for risk of cancers of the colon and rectum associated with homogeneous exposure to water source characteristics for 30 or more of the 40 years before the study, by sex

Water factor level	Males			Females		
	Cases	Controls	OR ^a (CI)	Cases	Controls	OR ^a (CI)
Colon cancer						
Source						
Ground	98	254	1.00	106	128	1.00
Chlorinated surface	231	472	1.49 (1.10–2.00)	166	197	0.79 (0.56–1.10)
THM level						
0–24 µg/liter	105	276	1.00	110	131	1.00
25–74	47	85	1.53 (0.99–2.38)	23	64	0.46 (0.26–0.81)
≥75	37	65	1.87 (1.15–3.05)	23	30	0.92 (0.49–1.71)
			<i>P</i> = 0.005			<i>P</i> = 0.211
Rectal cancer						
Source						
Ground	118	254	1.00	67	128	1.00
Chlorinated surface	177	472	0.99 (0.74–1.33)	145	197	1.09 (0.75–1.57)
THM level						
0–24 µg/liter	119	276	1.00	72	131	1.00
25–74	41	85	1.27 (0.81–2.00)	20	64	0.62 (0.34–1.13)
≥75	22	65	0.98 (0.56–1.72)	12	30	0.72 (0.34–1.53)
			<i>P</i> = 0.746			<i>P</i> = 0.180

^a OR (95% CI) for colon cancer adjusted for age; sex; education; body mass index; and intake of energy, cholesterol, calcium, alcohol, and coffee. OR (95% CI) for rectal cancer adjusted for age; sex; education; body mass index; previous medical conditions; and intake of energy, cholesterol, calcium, and coffee.

Table 4 ORs and 95% CIs for the association between colon cancer and cumulative exposure to CIs THMs by tap water consumption, among males^a

Tap water consumption	THM-years (µg/liter-yr)			
	<478	478–1502	1503–1946	>1946
<1.5 liter/day	1.00	1.13 (0.58–2.21)	1.30 (0.66–2.56)	2.14 (1.13–4.07)
1.5–2.05	1.43 (0.76–2.69)	1.78 (0.91–3.46)	0.98 (0.49–1.93)	1.45 (0.76–2.74)
>2.05	1.12 (0.58–2.18)	1.71 (0.90–3.24)	1.51 (0.80–2.87)	2.42 (1.28–4.56)

^a ORs (95% CI) adjusted for age; education; body mass index; and intake of energy, cholesterol, calcium, alcohol, and coffee.

CI, 6–29%). In contrast, among females, the risk of colon cancer was not positively associated with exposure to chlorination by-products. Inverse associations were observed in those exposed to a THM level of ≥50 g/liter for 20–34 years and in the highest quartile of THM-years.

In the analysis of rectal cancer, no associations with factors representing exposure to chlorination by-products were observed for either sex.

Homogeneous Water Exposures. Subjects used an average of 2.9 different water supplies during the 40-year exposure period. Therefore, in the preceding analyses, subjects within each duration category may have had a heterogeneous mixture of exposures as a result of living at residences with water sources that varied among the exposure categories over time. The analyses presented in Table 3 were restricted to those subjects who had homogeneous values for the exposures considered in an attempt to examine the effect of concentration of chlorination by-products while holding the duration of exposure constant. That is, only subjects who had exposures for at least 30 years within a single level of exposure (with respect to either ground *versus* chlorinated surface water or THM level in three categories) were included.

Among males, use of chlorinated surface water for at least 30 years was associated with a 49% increased risk of colon cancer relative to those served by ground water for at least 30 years (95% CI, 10–100%). Colon cancer risk also increased with THM concentration. Those exposed to a THM level of ≥75 µg/liter for ≥30 years had an 87% increase in risk com-

pared with those exposed to levels <25 µg/liter (95% CI, 15–205%). Among females, water source (chlorinated surface *versus* ground) was not associated with colon cancer risk. A reduced risk of colon cancer was observed for females exposed to THM concentrations between 25 and 75 µg/liter (OR, 0.46; 95% CI, 0.26–0.81), but not for those exposed to higher THM concentrations (OR, 0.92; 95% CI, 0.49–1.71). No associations were observed between these exposure factors and rectal cancer risk for either sex.

Risk by Volume of Water Consumed. Inclusion of a variable representing the quantity of water ingested provides an additional dimension of cumulative exposure to the analysis of exposure to chlorination by-products. An analysis was done to assess whether subjects who consumed greater volumes of water and had high cumulative THM exposure were at greater risk of colon or rectal cancer. Water consumption was categorized into three levels based on tertiles of the distribution within controls. The referent category for all ORs was comprised of those who consumed <1.5 liters/day and in the lowest quartile of THM-years.

Relative risks for colon cancer among males are reported in Table 4. Overall, the pattern of risk did not provide support for an interaction between volume of water consumed and cumulative THM exposure (*P* interaction > 0.05). However, the largest colon cancer risk among males was observed for those consuming high amounts of tap water with high cumulative THM exposure (OR, 2.42; 95% CI, 1.28–4.56). Analyses for female colon and rectal cancer risk were limited by the low

number of subjects in some strata and are not presented. No statistically significant relative risk estimates were observed, and patterns of relative risk were inconsistent.

Discussion

This study supports a relationship between colon cancer risk and exposure to chlorination by-products among males, but not among females. Among males, the magnitude of the relationship varied with the parameter used to represent exposure; risk estimates were stronger for duration of exposure to THMs than with duration of exposure to chlorinated surface water. When examining cumulative THM exposure, males in the highest quartile had 1.74 times the risk of those in the lowest quartile. No relationship was observed between rectal cancer risk in males or females and exposure to chlorination by-products.

Colon cancer has been found to be associated with water characteristics in some other studies using exposure to chlorinated surface water as the measure of by-product exposure. In ecological studies, age- and sex-adjusted cancer mortality and incidence rates of colon and rectal cancers have frequently been associated with characteristics of water supply systems (9, 10). Of five mortality case-control studies that examined both colon and rectal cancer and assessed exposure based on either residence at death (11–14) or more detailed residence information from supplementary data sources (15, 16), two found an association with colon cancer (11, 12) and one reported an association with rectal cancer (15, 16). A prospective cohort study of women that examined exposure to private well, ground, or surface water based on the residence at the time of entry into the cohort found an increased risk of colon cancer associated with use of surface water (17). One incident case-control study reported a significant elevation in colon cancer risk associated with chlorinated water among subjects >60 years of age (18).

Although levels of by-products are higher in chlorinated surface water supplies than ground water supplies, the levels of chlorination by-products in chlorinated surface water vary widely. We estimated summer THM level in an attempt to create a more specific measure of total chlorination by-product exposure. Therefore, more comparable to our study in methodology are two case-control studies that have obtained more comprehensive information by using THMs as a measurement of exposure and using incident cancer cases and subject interviews to ascertain residential histories, water exposures, and information about potential confounders (5, 19). These studies, in contrast to our study, observed colon cancer risk estimates with exposure to chlorinated surface water or THM levels that were close to the null (5, 19). Only one of these studies examined rectal cancer risk (5) and reported a more than doubling of risk for both sexes combined.

Associations between colon cancer risk and exposure to chlorination by-products in our study were observed for males, but not for females in contrast to other studies that did not find a sex difference (5), or studies of women only that found an increased risk of colon cancer (12, 17). However, other descriptive and analytical epidemiological findings suggest that colon cancer risk is influenced by gender. The observations that distal colon cancers occur more frequently in males than females (20, 21) and that different subsites may have different etiologies (22) suggest that the different sexes may have distinct risk factor profiles.

Because a high degree of correlation exists between each exposure measure used in this study, the individual analyses should not be considered wholly independent. However, several parameters of exposure to chlorination by-products were

used to help identify the most meaningful exposures. Duration of exposure was examined at several cutoffs of THM concentration to investigate whether the associations were stronger at higher levels, and our use of cumulative THM exposure was based on the assumption that it is the accumulation of a potential carcinogen that influences cancer risk. The strongest risk estimates for colon cancer among males were observed with ≥ 35 years of exposure to a THM level ≥ 75 $\mu\text{g}/\text{liter}$, and for the highest quartile of cumulative exposure. Restriction of the analysis dataset to those with relatively homogeneous exposures facilitated the examination of the effect of increasing THM level on risk while holding duration of exposure constant. The observed trend in colon cancer risk among males supports a dose-response relationship.

Perhaps the largest methodological limitation of this study is the representation of subject exposures. Possible sources of misclassification include the use of estimated historical THM levels and variation in individual behaviors not captured in this study that influence exposure. Because of the availability of historical treatment facility data, this study only considered exposures occurring over a 40-year time period, whereas other investigations have examined exposures of a longer duration (5). Incorporating volume of water consumed accounted for a further dimension of individual variation in oral exposure. However, this dimension of frequency was not captured for other routes of exposure (*e.g.*, inhalation and dermal) in this study. In addition, it is possible that total THMs correlate poorly with the important etiological agents in the chlorination by-product mixture.

A potential concern in this study is that a low proportion of potentially eligible cases were included in the analysis. Of 3252 colon and rectal cancer cases identified during the study, only 1399 (43%) are represented in the analysis. Case subjects were lost because of death and illness, their physician not providing consent or not responding to our requests, and refusal of the cases to participate. Study physicians and patients were not aware of the specific exposures of interest (*e.g.*, THM levels) and therefore, it is unlikely that those included and those not included differed systematically with respect to our exposure measure.

It is also a concern that case or control participation may be related to a correlate of THM level, such as county of residence. The distribution by residence county at diagnosis for participating colorectal cancer cases was compared with the distribution of cases identified in the Ontario Cancer Registry. These distributions were within 1% for each of the 39 counties in the study area. In a similar manner, the representativeness of control subjects was examined by comparing the percentage of controls residing in each county with that expected based on Canada census data (23). These distributions were similar with a difference of >1% occurring for only 2 of 39 counties. These observations suggest that a systematic selection of case or control subjects according to residence location did not occur.

The study was limited by incomplete water exposure history for some subjects. In particular, those residing outside the province of Ontario for a large number of years would have an incomplete water history. To minimize misclassification, the analysis was limited to those with at least 30 years of exposure information of the 40-year exposure time window. Of those subjects included in the analysis, the average number of years of water data was 38.1 for controls, 38.7 for colon cases, and 38.3 for rectal cases.

Chance and confounding must be considered when interpreting the results of this study. The observed association of exposure to chlorination by-products with colon cancer risk

among males but not among females was unexpected. It is possible that the excess risk observed in males was a chance finding. The potential confounding effects of several known risk factors were taken into account in the analyses, but the possibility remains that unknown or unmeasured risk factors may have biased the results. Urbanicity was a confounder in one previous investigation (5). In the present study, a proxy of urbanicity, the average population density of lifetime residences, was only weakly correlated with colon cancer risk and was not associated with rectal cancer risk. Adjustment for population density did not alter colon or rectal cancer risk estimates.

THMs were used in this study as a surrogate to represent exposure to chlorination by-products, and THMs themselves may not pose a health risk. Although chloroform accounts for a large proportion of the total THMs in most chlorinated water supplies, toxicological evidence suggests that other by-products, such as brominated by-products and haloacetic acids, may have greater carcinogenic potential (24, 25). Brominated by-products and haloacetic acids have been observed in Ontario water supplies and may be responsible for the observed effects in this study (26).

In summary, an excess risk of colon cancer among males was observed with long-term exposure to chlorination by-products. No association with exposure to chlorination by-products and risk of colon cancer was observed for females, nor of rectal cancer for males or females. These results are only partially congruent with the limited amount of literature addressing this issue.

Acknowledgments

We thank the participants of this study, physicians, study staff, and the staff of the water treatment facilities and of the Ontario Cancer Registry (at Cancer Care Ontario). We also thank Dr. Yang Mao and Robert Semenciw of the Cancer Bureau of the Laboratory Centre for Disease Control, Health Canada and Dr. Andy Gilman of the Great Lakes Health Effects Program, Health Canada.

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